PREOPERATIVE HISTOPATHOLOGICAL DIFFERENTATION OF INTRACRANIAL LESIONS WITH H^1 MR SPECTROSCOPY

Dissertation submitted to
M.Ch., (BRANCH II – NEUROSURGERY – 5 YEARS)

February – 2008

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,
CHENNAI, TAMILNADU.
DEPARTMENT OF NEUROLOGY & NEUROSURGERY,
MADURAI MEDICAL COLLEGE,
MADURAI.

CERTIFICATE

This is to certify that the dissertation entitled "**PREOPERATIVE HISTOPATHOLOGICAL DIFFERENTATION OF INTRACRANIAL LESIONS WITH H^1 MR SPECTROSCOPY**" submitted by **Dr. S. Vijay Kumar** to the Department of **Neurology and Neurosurgery** , The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.Ch. Degree (Neurosurgery) is a bonafide research work carried out by him under our direct supervision and guidance.

Dean,
Govt. Rajaji Hospital,
Madurai Medical College,
Madurai.

Prof. & HOD,
Department of Neurology
and Neurosurgery,
Govt. Rajaji Hospital,
Madurai Medical College,
Madurai.

DECLARATION

I, **S. Vijay Kumar**, solemnly declare that the dissertation titled "**PREOPERATIVE HISTOPATHOLOGICAL DIFFERENTATION OF INTRACRANIAL LESIONS WITH H^1 MR SPECTROSCOPY**" has been prepared by me.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University in partial fulfillment of rules and regulations for the M.Ch degree - Neurosurgery.

Place: Madurai,

Date: **Dr. S. VIJAY KUMAR**

ACKNOWLEDGEMENT

I sincerely thank **THE DEAN**, Madurai Medical College and Government Rajaji Hospital, Madurai for permitting me to do this dissertation.

I acknowledge with gratitude the dynamic guidance given to me by my **Prof. Dr. S.Manoharan**, Head of department of Neurology and Neurosurgery.

I sincerely thank, **Prof. Dr.D.Kailairajan**, and Prof**. Dr. N.Ashok Kumar**, Department of Neurology and Neurosurgery for their persistent encouragement.

I wish to thank the **Assistant Professors, Department of Neurology and NeuroSurgery**, who were always ready to render help whenever needed.

I take this opportunity to express my respect to **Prof. Dr.V.Inbasekaran**, & **Prof. V.G.Ramesh** for their guidance and untiring support.

CONTENTS

INTRODUCTION

MR spectroscopy provides a measure of brain chemistry. The most common nuclei that are used are ^{1}H (proton), ^{23}Na (sodium), ^{31}P (phosphorus). Proton spectroscopy is easier to perform and provides much higher signal-to-noise than either sodium or phosphorus. Magnetic resonance spectroscopy (MRS) has received little attention from the neurosurgeons because the results are obtained in graphs, not in pictures and until lately it required dedicated units and software.

Adequate MR Spectra may be obtained in periods of time as short as 10 to 15 minutes. Therefore, they may be added to routine MR imaging studies without significant time penalties. The MR spectra do not come labeled with the diagnosis. They require interpretation and should always be correlated with the MR images before making a final diagnosis. More over, MR spectroscopy provides greater information concerning tissue characterization than what is possible with MR imaging studies alone. We evaluated the utility of proton MR Spectroscopy in differentiating intracranial tumors with emphasis on differentiating ring enhancing lesions of the brain.

MR imaging has made it easier to detect and distinguish among intracranial mass lesions. Nevertheless, in some cases it is impossible to base a specific diagnosis solely on clinical and radiological findings. Thus biopsy has to be performed to provide a diagnosis as the basis for treatment regimens. Open biopsy is commonly used, and if possible, combined with open resection of the intracranial tumor. Lesions located in vital or eloquent parts of the brain, however, may be unsuitable for open neurosurgical intervention.

MR spectroscopy (MRS) is a technique that allows noninvasive monitoring of

metabolites within the tissue of interest, and has the potential for providing information about a lesion's composition and response to therapy. A number of water-suppressed proton (1H) MRS techniques have been developed for obtaining spectra from selected regions within the brain. These provide either a single-spectrum (single-voxel MRS) or a multidimensional array of spectra from the region of interest (multivoxel MRS imaging).

The purpose of this study was to evaluate the hypothesis that proton MR spectroscopy might be able to improve preoperative diagnostic accuracy in patients scheduled for biopsy of intracranial mass lesions and therefore obviate biopsy in some cases.

BASICS OF MAGNETIC RESONANCE SPECTROSCOPY

Spectroscopy based on nuclear magnetic resonance is used for analysis of molecules. MRS is a method to obtain NMR information regarding biochemical substances such as ATP, choline, lactic acid in vivo by collecting magnetic resonance signals from nuclei of biological substances such as P^{31} and H^{1} other than water and fat. Therefore, MRS provides molecular based information such as that concerning biochemical changes in the body, unlike histomorphological information derived from MRI.

RF COIL

Special radio frequency coils designated to measure different parts of the body are used to allow the corresponding area to generate magnetic resonance signals and to receive them. In this evaluation, MRS is performed using H^{1} as the nuclei. When MRS is performed using nuclei other then H^{1} like P^{31}, special frequency hardware becomes necessary because of difference in the resonance frequency. To obtain spectra signals, H1 MR images must be

obtained in advance and the region in which measurements are made must be targeted. The patients here are carefully immobilized to obtain high reproducibility.

LOCALISATION

Biochemical activities in the body occur unevenly at the microscopic level and different tissues e.g., normal tissue and malignant tissue exhibit different biochemical activities.

Without localizing the area in which magnetic resonance signals are to be collected, a variety of biochemical activities will commingle. Therefore, selection of the region in which signals are to be obtained is one of the keys to successful MRS. There are several methods for restricting signal reception. The use of surface coil, the three dimensional localization method by adding the positional information to the magnetic resonance signals using gradient magnetic field similar to that used in MRI is the one that is commonly employed. This three dimensional localizing method can be classified into single voxel spectroscopy, in which single region is excited selectively and multi voxel method, in which magnetic resonance spectra are examined from multiple voxels in a matrix.

SINGLE VOXEL METHOD

This method is a technique that makes a specified selected signal generate second spin echo. This method is otherwise called point resolved spectroscopy (PRESS). Radiofrequency pulse in a sequence of $90^{o} - 180^{o} - 180^{o}$ induces two spin echoes. Since the slice-selective gradient magnetic fields corresponding to each radiofrequency pulse are different, three perpendicular planes are usually selected. As a result, the part in which the three planes converge becomes the selected region since the second spin echo is generated selectively in

this region. The second spin echo region in which selected slices of three gradient magnetic fields intersect with one another is taken as the region selected for MRS. Also, the gradient magnetic fields applied before and after the timing of each 180° pulse to cancel the phase of spins other than those in the selected region are called spoiled gradient magnetic fields. Since the phase of spins in the selected region are reversed by 180° pulses, the phases of spins induced by spoiled gradient magnetic fields before and after the 180° pulse cancel and the signal is preserved.

STEAM (Stimulated Echo-Acquisition Mode)

This technique is used to induce stimulated echo signals exclusively from a given region. Stimulated echoes are generated by a sequence of 90° – 90° – 90° signals. Stimulated echo is different from spin echo in that, instead of 180° pulse, it employs two 90° pulses sandwiching the mixing time. Since the mixing time is independent, time to echo can be made relatively short. Therefore, compared with press, the time from initial excitation to the generation of signal echoes can be reduced for measurement of metabolites with short T_2.

The stimulated echo is explained qualitatively as follows. The phases of the spins induced by the first 90 ° pulse are distributed isotropically due to T^2 relaxation and spoiling gradient magnetic fields. After the second 90 ° pulse, half the information of the excited spins is preserved in the direction B_o (the z axis). Finally the preserved spin is transferred to the *xy* plane by the third 90 ° pulse and a stimulated echo is generated after TE similar to the spin echo. Since only half the information of the induced spin could be obtained, the signal intensity is smaller than in PRESS with a similar delay time. While two 180° pulses are employed in PRESS, the pulses used in STEAM are all 90 °. In addition the regional

selectivity is higher with 90 ° pulses. This is a major feature of STEAM. By contrast, the flip angle of 180° pulses used in PRESS must be carefully adjusted and radiofrequency coils with homogenous radiofrequency magnetic field are required.

MULTI VOXEL METHOD

The single voxel method provides information in only single selected region. The multivoxel method is used to simultaneously obtain spectra in multiple regions. In this method, the given field of view (FOV) is divided into several voxels and the spectrum is examined in each voxel. In this method, the number of voxels is relatively small compared with MRI, but the method is also called chemical shift imaging (CSI) because it is a variation of MRI.

As a general rule, the single voxel, short TE technique is used to make the initial diagnosis, because the signal-to-noise is high and all metabolites are represented. Multi voxel, long TE techniques are used to further characterize different regions of a mass and to assess brain parenchyma around or adjacent to the mass. Multi-voxel, long TE techniques are also used to assess response to therapy and to search for tumor recurrence.

SATURATION AND RELAXATION

The transition of nuclear spins into the hierarchical equilibrium state in the presence of an external magnetic field is not instantaneous but rather is governed by a first-order rate process. Once a nucleus reaches a higher energy state whether it is due to the external magnetic field or an RF pulse, there would be no further absorption of energy and soon the population difference between the two states would be zero. The system would thus reach saturation.

The only way the nuclei can remain accessible to further energy absorption is by a

mechanism of energy emission or loss. Nuclei do not collide easily and therefore, cannot lose energy as molecular, vibration, or translational loss. Nuclei lose their energy through resonance with the molecular motion of the lattice. Rotational and translational motions of molecules in liquids create fluctuating time-dependent magnetic fields. When the frequency of this fluctuating magnetic field equals the Larmor frequency, a magnetic torque is exerted to flip the orientation of the nuclei and thus their energy states. The magnetic energy received by the lattice is transferred into thermal energy.

Since this process of energy loss or relaxation is quite dependent on the molecular environment, different molecular environments encountered for H^1 will yield different rates of relaxation governed by their relaxation time, T_1. Thus, gray and white matter would have different rates of recovery of protons in the longitudinal plane.

The time dependence of the magnetization in the transverse plane after the RF resonance is affected by another relaxation time, i.e., the spin–spin relaxation time, T_2. As in the case of spin–lattice relaxation, the local fluctuating magnetic field due to the molecular motion also affects T2.

The phase coherence of the individual nuclear spins when exposed to the fluctuations along with the inhomogeneities in the external magnetic field results in a spread of their Larmor frequencies seen as a “fanning out” or loss of phase after which the spins move back to the axis of the external field as magnetization in the transverse plane goes to zero. This type of relaxation is different from longitudinal relaxation since the total energy of the spin system does not change.

THE CHEMICAL SHIFT

Earlier it was stated that the resonance frequency for nuclei is dependent on the

magnetic field experienced by the nuclei. One would hence expect the same nuclei in a compound to resonate at a single frequency. This, however, was found not to be the case soon after the discovery of NMR. Even a pure compound such as ethanol was found to have multiple frequency peaks.

Since the external magnetic field was homogeneous within the liquid, the explanation laid in differences in microscopic magnetic environments within the molecules as a result of which nuclei experienced variations in the effective magnetic field. These microscopic field variations arise from the electrons orbiting the nucleus and producing their own weak magnetic field. The s-electrons are spherically symmetric and circulate producing current, which in turn produces a magnetic field at the nucleus, which opposes the external magnetic field.

Thus, in order to obtain the resonance condition, it is necessary to increase the applied field over that for the isolated nucleus. If one nucleus is more shielded than another in the same external field, its signal will be shifted to a lower frequency. Because the strength of the induced field due to nuclear shielding is proportional to that of the applied field, we can define a constant, called the shielding or screening constant, which is sensitive to the chemical environment of the nuclei.

Therefore, nuclei in different chemical environments experience different fields and hence produce signals at different frequencies. This up field shift of the nucleus is called a *diamagnetic shift* and is present in every molecule since each has s-electrons. The electrons in p-orbit with no spherical symmetry produce magnetic fields that are large which when averaged over molecular motion give low-field shifts. This deshielding effect is called the *paramagnetic shift.* Of course, for protons with no p-electrons there is no paramagnetic term.

Thus, the practical implication is that the differences in the resonance frequencies

between different nuclei range in millions of hertz (Hz) and the spread of resonance frequencies for a single nucleus is in the range of a few thousands of hertz due to this chemical shift. The electronic screening is due not only to the electrons from the nucleus' own electronic cloud but also to differences in chemical bonds between various atoms and their different electron distributions.

Thus, hydrogen bonded to carbon experiences a different "electron field" than hydrogen bonded to oxygen. In addition, the types of bonds (single, double) influence the field. Spectroscopy is then this extraction of the shift in frequencies from the NMR signal, which clues one to shifts or differences in the molecular structure of tissues. While the chemical shift may introduce artifacts in NMR imaging; it is the basis of spectroscopy.

In this way, the chemical shift is normalized with respect to the operating frequency and is independent of the external magnetic field, making comparison of data easy and simple.

WATER SUPPRESSION

In proton MRS, the amount of H^1 in water is overwhelmingly greater than that of metabolites such as lactic acid and NAA. Therefore magnetic resonance signals from H^1 in water must be suppressed.

CHESS (Chemical Shift Selective) is a method used to achieve this. This sequence is placed above the pulse sequence for localization of the nuclei. In this sequence suppression of radiofrequency pulse has narrow resonance frequency of water and has a narrow band that does not overlap the frequency of H^1 in each metabolite. A gradient magnetic field follows the suppression of radiofrequency pulse to cancel out the direction of the spins.

Selective T_1 Relaxation

An inversion recovery scheme can be used for water suppression since the water T1 may be significantly different from other metabolites. The magnetization is first inverted with a 180° pulse. After a time, the longitudinal magnetization recovers. The water magnetization is null at a time when other molecules are partially or completely relaxed and the sampling pulse can be generated. This sequence, however, has the drawback of requiring long TD since water T1 is long. In addition, it is also difficult to quantitate since the metabolites may be only partially relaxed.

RECEPTION OF SIGNALS AND RF DETECTION

After the radio frequency signals from various substances, including the metabolites with different resonant frequencies according to the differences in the chemical shift are

received with a radiofrequency coil, they are amplified by a preamplifier and detected as low frequency components by two phase detectors.

Detection occurs by picking a lower frequency from the entire frequency by eliminating the reference radiofrequency of the apparatus. In a 1.5 Tesla MRI with a standard radiofrequency of 64 MHz, the bandwidth of signals detected is usually 640 Hz or less because the spectral band of H^1 MRS is about 10ppm. This conversion to a lower frequency allows analogue-digital conversion of signals and the data can be processed by a computer.

DATA PROCESSING

After the FID is collected in the time domain, it needs to be conditioned, corrected, and transformed into the frequency domain to see the chemical shift of the metabolites. This transformation is brought about by a mathematical operation called Fourier transformation.

Zero Filling

Some manipulations are done to the FID in the time domain before performing Fourier transformation. It is preferable to increase the number of complex data points by a technique called zero filling. It consists of extending the experimental time domain data set by a number of zeroes. This has a similar effect as increasing the sampling points after the signal has decayed. It results in a smooth interpolation between the spectral data points and improves the appearance of the spectrum after Fourier transformation

Apodization

Apodization means "cutting the feet off." It indicates a mathematical operation by which all of the data points of the FID are multiplied by a function characterized by a starting value of 1 and that decays regularly to zero at the end of the acquisition time.

OBSERVED METABOLITES AND THEIR SIGNIFICANCE

There is evidence that the concentration of normal metabolites in the brain varies according to the patient's age. This variation is more noticeable during the first 3 years of life but may be seen up to 16 years of age. The most striking variation is an increase in NAA/Cr ratio and a decrease in the Cho/Cr ratio as the brain matures. These changes may reflect neuronal maturation and an increase in the number of axons, dendrites, and synapses.

N-Acetyl-L-aspartate (NAA)

The presence of NAA is attributable to its *N*-acetyl methyl group, which resonates at 2.0ppm. This peak also contains contributions from less important *N*-acetyl groups. NAA is accepted as a neuronal marker, its concentration will decrease with many insults to the brain.[31] The role of NAA in the brain is unknown. *N*-Acetyl-aspartyl-glutamate (NAAG) is co localized with NAA in neurons and releases NAA and glutamate when it is cleaved by N-acetylated alpha-linked dipeptidase.[39] Breakdown of N-acetyl-aspartyl glutamate releases both NAA and glutamate and subsequent breakdown of NAA leads to aspartate. These compounds are excitatory amino acids and are increased with ischemia. NAA is not present in tumors outside the central nervous system. In normal spectra, NAA is the largest peak.

Choline (Cho)

The peak for Choline occurs at 3.2 ppm. It contains contributions from glycerophosphocholine, phosphocholine, phosphatidylcholine and therefore reflects total brain choline stores. Choline is a constituent of the phospholipid metabolism of cell membranes and reflects membrane turnover, and it is a precursor for acetylcholine and phosphatidylcholine. Acetylcholine is a neurotransmitter that is critical for many aspects of memory, cognition, and

mood.

Creatinine (Cr)

The peak for Cr is seen at 3.03 ppm and contains contributions from Cr, Cr phosphate, and, to a lesser degree, gamma-amino butyric acid, lysine, and glutathione.[23] An additional peak for Cr may be visible at 3.94 ppm. Therefore, the Cr peak is sometimes referred to as "total Cr." Cr probably plays a role in maintaining energy-dependent systems in brain cells by serving as a reserve for high energy phosphates and as a buffer in adenosine triphosphate and adenosine diphosphate reservoirs. Cr is increased in hypo metabolic states and decreased in hyper metabolic states. In normal spectra, Cr is located to the immediate right of Cho and is the third-highest peak. Because this peak remains fairly stable even in face of disease, it may be used as a control value.

Lactate

The lactate peak has a particular configuration. It consists of two distinct, resonant peaks called a "doublet" and is caused by the magnetic field interactions between adjacent protons (J coupling). This lactate doublet occurs at 1.32 ppm. A second peak for lactate occurs at 4.1 ppm. Because this latter peak is very close to the water, it is generally suppressed. Normally lactate levels in the brain are low. The presence of lactate generally indicates that the normal cellular oxidative respiration mechanism is no longer in effect, and that carbohydrate catabolism is taking place.[40] Lactate can play a role as a neuromodulator by altering the excitability of local neurons.

Myoinositol

Myoinositol is a metabolite involved in hormone sensitive neuroreception and is a

possible precursor of glucuronic acid, which detoxifies xenobiotics by conjugation.[48] The myoinositol peak occurs at 3.56 ppm.

Glutamate and Glutamine

Glutamate is an excitatory neurotransmitter which plays a role in mitochondrial metabolism. Gamma-amino butyric acid is an important product of glutamate. Glutamine plays a role in detoxification and regulation of neurotransmitter activities.[30] These two metabolites resonate closely together and they are commonly represented by their sum as peaks located between 2.1 and 2.5 ppm.

Alanine

Alanine is a nonessential amino acid whose function is uncertain. Its peak occurs between 1.3 and 1.4 ppm and therefore may be overshadowed by the presence of lactate.

Lipids

Membrane lipids in the brain have very short relaxation times and are normally not observed unless very short TEs are used. The protons of lipids produce peaks at 0.8, 1.2, 1.5 and 6.0 ppm.[6] These peaks comprise methyl, methylene, allelic, and the vinyl protons of unsaturated fatty acids. These metabolites may be increased in high-grade astrocytomas and meningiomas and may reflect necrotic processes. However, it is also important to remember that normal lipid resonances arising from fat may be the result of voxel contamination by fat located in the subcutaneous scalp.

CLINICAL APPLICATIONS OF MRS IN NEUROSURGERY

Astrocytomas

Proton MR Spectroscopy readily distinguishes normal brain tissues from astrocytomas.[5,13,26] However, proton MR spectroscopy may not be able to distinguish between different histological grades of malignancy in astrocytomas. Some investigators have proposed that the presence of lactate correlates with a higher degree of malignancy and that it is commonly observed in glioblastoma multiforme.[10,12]

The typical Proton MR Spectroscopic characteristics of astrocytomas include a significant reduction in NAA, a moderate reduction in Cr, and an elevation of Cho. Reduction of NAA probably indicates a loss of normal neuronal elements as they are destroyed and/or substituted by malignant cells. In astrocytomas, the NAA is reduced to 40% to 70% of that in normal brain. Reduction of Cr is probably related to an altered metabolism, and elevation of Cho may reflect increased membrane synthesis and cellularity (both of which are present in tumors). Elevation of lactate may reflect tumor hypoxia. The Cho peak also is increased in the malignant astrocytomas. MR spectroscopy may be used to distinguish infection from a tumor, because the former has extremely low concentrations of Cho. Proton MR Spectroscopy may also play a role in monitoring the response of astrocytomas to treatment. In some instances, proton MR spectroscopy may detect tumor recurrence before MR images become abnormal.

Differentiation between gliomatosis cerebri and low grade glioma on anatomical grounds is difficult. There are, however, subtle MRS variations which may be helpful. Gliomatosis cerebri shows increased levels of creatine compared to low to normal concentration in low grade glioma. There are no significant differences in levels of Cho, NAA and myoinositol.

Metastases

In adults with multiple brain lesions the primary differential diagnosis is that of metastases. In the presence of a single lesion, differentiating between primary and secondary brain tumors is important but not often possible.[24,35] Metastases commonly show moderate to marked reduction of NAA, a decreased Cr signal, and elevated Cho.

These features are identical to those present in astrocytomas. Some metastases (particularly those from breast carcinomas[41]) may also contain lipids. Lipid resonance may also be present in high grade astrocytomas and is caused by the presence of necrosis.

Radiation Injury

Histologically, radiation injury is characterized by damage to the vascular endothelium that may result in ischemia and necrosis. MR spectroscopy shows elevation of lactate in patients who have received 40 Gy or more to the brain. This abnormality is appreciable even when the MR imaging studies are normal. Therefore, proton MR spectroscopy may be promising as a tool for the detection of radiation injury before it becomes evident by MR imaging. Radiation necrosis may be indistinguishable from residual and recurrent tumors by computed tomography.

Patients with radiation necrosis showed highly depressed levels of NAA, Cho, and Cr and an intense and broad peak between 0 and 2.0 ppm. This peak is consistent with tissue necrosis. This cellular breakdown peak probably consists of free fatty acids, lactate, and amino acids. Elevated lactate, reflecting severe tissue ischemia and/or mitochondrial damage, will be present in these patients.[14]

Meningiomas

Because meningiomas arise outside the central nervous system, theoretically they do not contain NAA. The signal of Cho is, however, markedly increased (up 300 times normal) particularly in recurrent meningiomas. Lactate and alanine may be also elevated in some meningiomas. There is no clear explanation for the increase in alanine in meningiomas. The above proton MR spectroscopic features are seen in typical meningiomas (fibrous type).

Multiple Sclerosis

MR images with contrast will show enhancement in active multiple sclerosis lesions. It has been shown that NAA is decreased in patients with chronic multiple sclerosis in whom axonal loss has occurred. Conversely, in acute plaques, NAA may be normal, indicating that the axons have not yet disappeared or have been permanently damaged.[1,2] In addition, resonances corresponding to free lipids (0.9 to 1.6 ppm) have been observed in chronic multiple sclerosis plaques and may reflect disintegration of myelin.

Infections

Brain abscesses typically show reduced levels of Cho, NAA and Cr. MRS can be used to distinguish pyogenic from tuberculous brain abscess. Pyogenic abscesses usually show increased amino acid (valine, leucine, isoleucine) peaks due to prominent proteolysis, while tuberculous abscess predominantly gives a lipid peak. Intracranial tuberculoma shows lipid resonance at 1.3 ppm, 2.02 ppm, and 3.7 ppm at in vivo MR spectroscopy.[16]

REVIEW OF LITERATURE

Several studies have been published regarding the use of proton magnetic resonance spectroscopy in characterization of brain tumors. But only few studies are available in distinguishing the ring enhancing lesions of the brain with MRS.

Classification of brain tumors using short echo time ^{1}H MR Spectra:

Devos A, Lukas L et al [11]

The purpose was to objectively compare the application of several techniques and the use of several input features for brain tumor classification using Magnetic Resonance Spectroscopy (MRS). The area under the receiver operating characteristic curve (AUC) was used to measure the performance of binary classifiers, while the percentage of correct classifications was used to evaluate the multi class classifiers. The influence of several factors on the classification performance has been tested: L2- vs. water normalization, magnitude vs. real spectra and baseline correction. Using L2-normalized complete spectra the automated binary classifiers reached a mean test AUC of more than 0.95, except for glioblastomas vs. metastases. This indicates that data acquisition and processing can be simplified for classification purposes, excluding the need for separate water signal acquisition, baseline correction and phasing.

Noninvasive magnetic resonance spectroscopic imaging biomarkers to predict the clinical grade of pediatric brain tumors:

Astrakas LG et al

This study evaluated the proton magnetic resonance spectroscopic imaging exams for 66 children with brain tumors. Neuro pathological grading was done with WHO criteria. Normalized Cho and lipids and/or lactate were elevated in high-grade (n = 23) versus low-grade (n = 43) tumors, which were confirmed by means of multiple logistic regression as independent predictors of tumor grade. Proton magnetic resonance spectroscopic imaging, although not a proxy for histology, provides noninvasive, in vivo biomarkers for predicting clinical grades of pediatric brain tumors.

Automated classification of short echo time in vivo 1H brain tumor spectra: a multi center study:

Tate AR, Majós C et al [45]

Automated pattern recognition techniques are needed to help radiologists categorize MRS data of brain tumors according to histological types and grades. A subset of 144 histo pathologically validated brain tumor spectra in the INTERPRET database, obtained from three of the collaborating centers, were grouped into meningiomas, low-grade astrocytomas, and "aggressive tumors" According to this study pattern recognition algorithms were less sensitive to acquisition parameters than had been expected.

1H-MR Spectroscopy of brain tumors in the course of radiation therapy: Use of fast spectroscopic imaging and single-voxel spectroscopy for diagnosing recurrence:

Träber F et al. [46]

54 patients with malignant brain tumor (44 cases of glioblastoma, 10 other high-grade gliomas) were examined post-surgically in a total of 140 proton MRS examinations in the course of radiotherapy and in follow-up controls. In all these cases MRS diagnosis was

confirmed histologically or by short-term follow-up. However, in 6 of 15 patients showing a normal choline pattern in the TSI acquisition, tumor recurrence appeared within three months. SVS provided early recognition of recurrent tumor when detecting characteristic alterations of metabolite concentrations in therapy follow-up.

Histopathological validation of a three-dimensional magnetic resonance spectroscopy index as a predictor of tumor presence:

McKnight TR et al [29]

This study was done by comparing data obtained preoperatively from proton magnetic resonance spectroscopy with the results of histopathological assays of tissue biopsies obtained during surgery to verify the sensitivity and specificity of a choline-containing compound-N-acetylaspartate index (CNI), which was used to distinguish tumor from nontumorous tissue within T2-hyperintense and contrast-enhancing lesions of patients with untreated gliomas. Biopsy samples containing tumor were distinguished from those containing a mixture of normal, edematous, gliotic, and necrotic tissue with 90% sensitivity and 86% specificity by using a CNI threshold of 2.5. On an average, one third to one half of the T2-hyperintense lesion outside the contrast-enhancing lesion contained CNI greater than 2.5.

Correlation of magnetic resonance spectroscopic and growth characteristics within Grades II and III gliomas;

McKnight TR at al [28]

In this study, patients with presumed Grades II or III glioma underwent 3D MR spectroscopic imaging prior to surgery, and two or three regions within the tumor were targeted for biopsy retrieval based on their spectroscopic features. The authors found that the

relative levels of Cho and N-acetylaspartate (NAA) correlated with the cell density.. The association was stronger in tumors with large ranges of Cho/NAA values, irrespective of the presence of contrast enhancement. The findings demonstrate the validity of using MR spectroscopy to identify regions of aggressive growth in presumed Grade II or III gliomas that would be suitable targets for retrieving diagnostic biopsy specimens.

Role of diffusion-weighted imaging and in vivo proton magnetic resonance spectroscopy in the differential diagnosis of ring-enhancing intracranial cystic mass lesions:

Mishra AM at al

In this study apparent diffusion coefficient values in 21 patients with abscesses were observed within the range of defined criteria, whereas in 8 patients, ADC values were beyond the range of defined criteria. Lactate and AAs with or without other metabolites were observed in 25 of 29 cases of abscesses on PMRS. Demonstration of restricted diffusion on DWI with reduced ADC is highly suggestive of brain abscess; however, in the absence of restriction, PMRS is mandatory to distinguish brain abscesses from cystic tumors.

Clinical application of proton magnetic resonance spectroscopy in the diagnosis of intracranial mass lesions:

Möller-Hartmann W et al [33]

This study was done to evaluate the clinical utility of 1H-MRS added to MRI for the differentiation of intracranial neoplastic and non-neoplastic mass lesions. 176 mostly histologically verified lesions were studied with a constant clinically available single volume 1H-MRS protocol following routine MRI. This study shows that spectroscopy added to MRI helps in tissue characterization of intracranial mass lesions, thereby leading to an improved

diagnosis of focal brain disease.

Proton magnetic resonance spectroscopy of human brain tumors: assessment of differences between tumor types and its applicability in brain tumor categorization.

Majós C, Alonso J et al [27]

This study was done to evaluate the usefulness of proton magnetic resonance spectroscopy in categorizing brain tumors. Differences in at least two resonances were found in all pair wise comparisons of tumor groups except in GBM vs. MET. Large lipid resonance was found to be characteristic of GBM and MET, and alanine was characteristic of MEN. Significant differences were found between LGA and AA in choline-containing compounds and total creatine resonances. These findings correctly classified 84% (21 of 25) tumors in the independent test set. Some additional utility was found in glycine/myo-inositol at 3.55 ppm for bilateral differentiation between GBM and MET. MRS provides useful information to categorize the most common brain tumors that can be implemented in clinical practice with satisfactory results.

AIMS AND OBJECTIVES

The first aim of this study is to evaluate the value of ^{1}H-MR spectroscopy for characterizing brain tumors.

The second aim of this study is to analyze the usefulness of MR spectroscopy in differentiating the ring enhancing lesions of the brain.

The third aim of this study is to assess the differences between the tumor types and its applicability in brain tumor categorization.

The fourth aim is to find out the effect of single voxel proton MR spectroscopic findings on treatment decisions.

MATERIALS & METHODS

STUDY PATTERN

This is a prospective study done over a period of two years on patients admitted in the Neurosurgery ward, Department of Neurology and Neurosurgery at Government Rajaji Hospital, Madurai with intracranial mass lesion for whom MR spectroscopy was taken.

EXCLUSION CRITERIA

Patients with poor quality scans were not taken into the study.

Patients with incomplete dataset for MRS.

Patients with MR Spectroscopy done with Phosphorus or Carbon are excluded from the study since this study is done exclusively with Proton MR spectroscopy.

Patients with congenital cystic lesions.

REASONS FOR EXCLUSION

This study is done exclusively to determine the role of proton MR Spectroscopy in differentiating brain tumors. This study does not include congenital cystic lesions for the fact that spectroscopy has limited value in congenital cystic lesions.

INCLUSION CRITERIA

Since our institution does not have the facility for MR spectroscopy, all patients admitted with MRI films T1W, T2W, T1W contrast and MRS were included in the study.

Patients examined only with Single voxel spectroscopy were also included in the evaluation of distribution patterns of abnormal spectra.

METHODS

Patient Population

The patients admitted in the Neurosurgical ward in the age group of 5 - 80 yrs with evidence suggestive of intracranial space occupying lesions will be studied on Magnetic Resonance Spectroscopy on a 1.5 Tesla MR unit. All the patients with mass lesions scheduled for surgery were recruited into the study. All patients underwent a preoperative workup adapted to the individual's clinical history and situation.

CT, MR Imaging, and MR Spectroscopic Measurements

Preoperative CT scans with contrast were obtained in all patients to look for ring enhancement. MRI scan with T1 W, T2 W, T1 with contrast were obtained along with MR spectroscopy for characterization of intracranial lesions. Particular interest was shown towards contrast enhancing lesions on CT Brain for evaluation under MR spectroscopy.

Some of our patients had two dimensional chemical-shift proton MR spectroscopy (multi voxel spectroscopy) that allows the mapping of metabolite concentrations to be manipulated by computer and superimposed on the image of an abnormality illustrating the distribution of such metabolites within the area of intracranial space occupying lesion. Rest of them had single voxel spectroscopy owing to the limitation of obtaining MRS from different radiological centers. Single voxel spectroscopy obtained from the mass lesion, the contra lateral normal brain parenchyma and the signal from the metabolites in the brain were analyzed. The metabolites that were used for analysis were N-acetyl aspartate (NAA), choline

(Cho), creatinine (Cr), lactate, alanine, glutamate and lipids. The variations in the Cho/Cr ratio and NAA/Cr ratio were noted.

The radiologist's diagnoses based on MR Spectroscopy were noted. Histopathological examinations of the intracranial lesion were studied. In case of suspected tuberculomas where HPE was not done, the response to ATT drugs and the resolution of the tuberculoma on follow up CT Brain contrast study were taken into account. In our study the emphasis was laid on the differentiation of various ring enhancing lesions on CT Brain contrast study with the help of MR Spectroscopy. MR Spectroscopy obtained with both PRESS and STEAM were obtained for analysis.

Intraoperative Tissue Specimen Collection and Pathological Examination

At the time of surgery biopsy specimens which typically measured 3*3*3 mm^3 were taken for each patient from the site of intracranial mass lesion. Each tissue sample was then taken with small surgical forceps and labeled and handled separately. Biopsy specimens were fixed in formalin after removal and were submitted for routine hematoxylin eosin pathologic examination. The surgical biopsy specimens taken for this study were examined by a pathologist. The tumor grade assigned using the World Health Organization criteria for classification of brain tumors was used.

Evaluation of MR Spectroscopy

MR spectroscopic results were evaluated for the distribution of pathologic spectra across the lesion and neighboring neuroradiologically normal-appearing tissue and for signal ratios in different tumor types. Substances of interest regarding the calculation of signal ratios in different tumor types were as follows: NAA 2.0 ppm; Cho 3.2 ppm; creatine and

phosphocreatine (Cr) 3.0 ppm; lipid-containing compounds and/or lactate (Lip-Lac), 0.9 to 1.3 ppm. Signal ratios were calculated for NAA/Cr, Cr/Cho. Only spectra with a clean baseline and narrow, visually distinct peaks were used for the metabolite ratio calculation.

The proposed diagnoses and accuracy based on MR spectroscopy were compared with histopathological findings and the usefulness of MRS in differentiating ring enhancing lesions of the brain was evaluated.

Statistical Analysis

In this study student t test was used for tumour groups for values of choline, NAA, creatine, myo-inositol, lipid peak, aminoacids, cho/cr ratio and statistical significance was found. The null hypothesis was rejected when p value was less than 0.05 and the results were considered statistically significant.

RESULTS

The data from 50 patients, including spectra and biopsy results, constitute our findings.

The tumor types investigated in our study are shown in table.

Tumour type	No of cases
Low grade glioma (WHO Grade I &II)	**9**
Anaplastic astrocytoma	**6**
Glioblastoma	**4**
Metastasis	**6**
Meningioma	**4**
Pyogenic abscess	**3**
Tuberculoma	**3**
Miscellaneous	**15**
Lymphoma	**2**
Ependymoma	**5**
Medulloblastoma	**3**
Germinoma	**2**
Chordoma	1
Multiple sclerosis	1
Epidermoid	1
Resolving hematoma	

The value of the observed metabolite peaks along with their ratios were recorded for each tumor type. The strongest group differences were seen for choline, choline/creatine ratio,

alanine and lactate peaks. Presence of decreased myo-inositol levels signified glioblastoma differentiating it from anaplastic astrocytoma.

The numerical data are summarized as follows.

Tumour Type	Cho	Cho/Cr	NAA
Low grade Glioma	3.11	3.07	1.16
Anaplastic Astrocytoma	2.98	3.85	0.54
GBM	3.77	5.27	0.86
Metastasis	3.07	4.01	0.41
Meningioma	3.59	8.18	0.22
Pyogenic abscess	0.73	2.26	0.38
Tuberculoma	0.44	1.5	0.30
Control subjects	1.07	1.30	1.93
P value	0.0020	0.0154	0.0012

The results thus obtained were statistically significant

^{1}H MRS metabolic changes observed in the major brain tumours

Major Tumor types	Cho	Cho/ cr	mI	NAA	LIP Lactate peak	AA peak	Alanine peak
Low grade Glioma	↑	↑	-	↓↔	-	-	-
Anaplastic	↑	↑	-	↓↓	↑	-	-

astrocytoma							
GBM	↑	↑	↓	↓	↑↑	↑	-
Secondaries	↑	↑	↓	↓↓	↑↑	↑	-
Meningiomas	↑	↑	-	↓↓↓	-	-	↑↑
Abscess	↓	↓	↑	↓↓↓	↑	↑	-
Tuberculoma	↓	↔	-	↓↓↓	↑↑	-	-

LOW GRADE GLIOMA

Our study had 9 cases of low grade gliomas classified radiologically which includes Histopathological WHO grades 1 & 2. All of these showed an increase in cho and an increase in cho/cr ratio. Lipids and myo inositol were absent. NAA showed a mild decrease in value. A single case showed the presence of amino acids. All the 9 cases were confirmed with their histopathologic findings. However, a case was reported as sub ependymal giant cell astrocytoma which was later classified as ependymoma based on Histopathological findings.

ANAPLASTIC ASTROCYTOMA

There were 6 cases of anaplastic astrocytoma in our study. All of them showed an increase in cho & cho/cr. A decrease in NAA was noted. Lipid peak was present in 5/6 cases and myo-inositol was absent in all cases. Amino acids were present in 2 cases. All the cases were confirmed by histopathology. There was no diagnostic error.

GLIOBLASTOMA

There were 3 cases of GBM in our study. All of them showed an increase in cho & cho/cr. A decrease in NAA was noted. Myoinositol was characteristically decreased in all 3 cases. Lipid peaks were present in all 3 cases. Amino acids were elevated in 2/3 cases. All 3 cases were confirmed by histopatology and there was no error in preoperative diagnosis.

There was also a case which was diagnosed as high grade glioma by MRS and was later shown to be a ependymoma by histo pathology.

METASTASIS

There were 6 cases of metastasis in our study. All of them had elevated cho & cho/cr and decreased NAA. Lipid lactate peak was noted in all 6 cases. Myo-inositol and amino acids were present in 2 cases..

Though the MRS presentation of secondaries is similar to GBM except for the consistent low levels of myoinositol in GBM , we did not have any diagnostic confusion since in all 6 cases the primary was known prior to MRS.

MENINGIOMAS

We had 4 cases of meningiomas. All showed decrease in cho, NAA, cho/cr & NAA/cr. Alanine peak was characteristically noted in all 4 cases of meningiomas. They are considered MRS signatures of meningiomas. All cases were confirmed by histopathology.

ABSCESS

Our study had 3 cases of abscess which showed a decrease in cho, cho/cr, NAA, NAA/ Cr. Amino acids were present in all 3 cases. Lipid lactate and myoinositol were elevated in 2 cases each. Since we did not encounter tubercular abscess, the differentiation between tubercular and pyogenic could not be classified.

TUBERCULOMA

Our study had 3 cases of tuberculoma which showed decrease in the levels of cho, cho/cr, NAA, NAA/cr. Lipid, lactate was elevated in 2/3 cases. The diagnosis was aided by T2 central hypointensity characteristic of tuberculomas on MRI. All of them were treated with Anti tuberculous therapy and showed resolution of edema, mass and ring enchancement on the 2^{nd} month.

MISCELLANEOUS

Ependymoma

There were 5 cases of ependymoma in our study which showed choline peaks with reduced creatine. Cases of ependymoma cannot be diagnosed with specific patterns seen on MRS and differentiation between ependymoma and medulloblastoma was not distinct with help of SVS.

Lymphoma

2 cases that we had showed elevated choline and markedly reduced NAA with prominent lipid lactate peaks characteristic for lymphomas.

Summary of results

Out of the total 50 cases, 44 cases were diagnosed correctly with imaging based on MRI and MRS which correlated with histopathology. This gives MRS, a sensitivity of 88% based on our study. Out of the 21 cases diagnosed as gliomas, 2 ependymomas were over diagnosed and later reclassified, which comes to a diagnostic accuracy of 90.4%.

However there was no diagnostic confusion in differentiating a tumor from infection with the help of MRS which gives it 100% accuracy.

Differentiation among various grades of gliomas were possible with characteristic markers on MRS which typically showed decreased myoinositol in GBMs, lipid lactate peaks in Anaplastic astrocytomas and with only elevated cho, cho/cr without lipid lactate or changes in myoinositol levels in low grade gliomas. Differentiating metastasis from high grade gliomas was not possible with MRS alone.

DISCUSSION

Spectroscopy is the art of eliciting information without appreciably changing the source of information. The information is obtained by perturbing the phenomenon under study and then observing its behavior as it attempts to cope with the perturbation. Most spectroscopes deal with the interaction of electromagnetic radiation with matter.

The different frequencies of electromagnetic radiation used as the probes affect matter differently and reflect different characteristics of matter, e.g., X-ray spectroscopy gives us information on the energy changes in the inner electrons of atoms or molecules, visible and ultraviolet spectroscopy informs us of the transitions in valence electrons, whereas microwave and infrared spectroscopy tells us of molecular and vibration energy transitions of molecules.

The Heisenberg uncertainty principle, however, ensures that the closer we approach the microscopic or quantum world, the less likely it is that our assumption of negligible effect will hold. Yet, as the state of the art in biomedical physics improves, increasingly we are realizing that to alter the story of any disorder or disease, understanding and intervention must take place at the molecular and genetic level. NMR spectroscopy is one such tool employed to understand the biochemical mechanisms of the human body in normal and diseased states. The technology provides a basis to model and interpret the macroscopic clues manifested as clinical and laboratory findings. The RF region of electromagnetic radiation corresponds to the transition in energy levels of the magnetic states of the atomic nuclei. Because the same

nucleus in different molecular structures may show different magnetic states, MRS can be applied to determine molecular structures.

Magnetic Resonance Spectroscopy (MRS) is a proven and useful method for the evaluation, assessment of severity, therapeutic planning, post-therapeutic monitoring and follow-up of diseases of the brain and other regions of the body.

In the clinical setting, diagnosis of intracranial mass lesions can be complicated by ambiguous neuro radiological findings, uncharacteristic clinical symptoms or symptom onset. In these cases, additional diagnostic methods are solicited, and MR spectroscopy might, at least when dealing with some specific diagnostic problems, be able to increase diagnostic accuracy by adding another piece to the diagnostic puzzle. When discussing spectroscopic data of brain lesions, the significance of calculation of signal ratios and the use of these ratios for determining the degree of tumor malignancy or for characterizing histological tumor types or subtypes is often stressed.[3,10,25,36,44]

When conventional imaging by magnetic resonance imaging (MRI) or computed tomography (CT) is inadequate to answer specific clinical questions, MR Spectroscopy is indicated to help in the diagnosis of intracranial lesions. MR Spectroscopy provides a measure of brain chemistry. Proton spectroscopy is easier to perform and provides much higher signal-to-noise than either sodium or phosphorus. Proton MRS can be performed within 10-15 minutes and can be added on to conventional MR imaging protocols. It can be used to serially monitor biochemical changes in tumors, stroke, epilepsy, metabolic disorders, infections, and neurodegenerative diseases. The MR spectra do not come labeled with diagnoses. They require interpretation and should always be correlated with the MR images before making a final

diagnosis.

Magnetic resonance spectroscopy (MRS) is a noninvasive technique which provides chemical information of metabolites present in living tissue and can be used to help characterize human brain tumors. A histopathological analysis of a biopsy is the present gold standard for diagnosis of an abnormal brain mass suspected of being a brain tumor. A biopsy is not without risk of morbidity and mortality and cannot be carried out in all instances (e.g., brain stem tumors). MRS has the potential to improve the diagnosis of brain tumors, with no additional risk to the patient. Several studies have already shown progress in automated pattern recognition for brain tumor classification based on MRS data.

Rand et al[38] described an analysis of visual inspection of single-voxel spectra at 0.5 T with a diagnostic accuracy of 0.96 in distinguishing neoplastic from nonneoplastic lesions. Multi voxel methods can be useful if the goal is to obtain a metabolic map of a large lesion or brain region. Pruel et al[37] were able to correctly classify 104 of 105 tumor spectra. With the use of multivoxel techniques, voxels containing viable tumor can be identified. However, unless spectral resolution is sacrificed, the acquisition times for multivoxel spectroscopy can be prohibitively long.

In single-voxel spectroscopy, the voxel placement is critical to the examination. For this reason, we chose to undertake spectroscopy after a contrast enhanced MR imaging series had been obtained, as this allows for precise voxel placement over an enhancing region so that signal is acquired only from viable tumor tissue. [21,38,43]

The optimal pulse sequence parameters for tumor grading are still an issue of debate. We have collected MR Spectroscopy done with both STEAM and PULSE sequences and most of our collections include single voxel spectroscopy done over the tumor tissue. Optimum

methods for standardization of in vivo proton spectra are also a matter of debate. The method most commonly used is that of taking the ratio of one peak area to another.[15,35,42] Another approach is to determine carefully the metabolic concentrations in units of mmol/L or weight of brain. In all the scans that we had collected, radiologists had chosen only peak ratios probably because of the simplicity of the method.

From the observation of our cases, it was studied that MR Spectroscopy has been of valuable help in differentiating intracranial lesions. Many studies have been done to validate the use of MR Spectroscopy in differentiating brain tumors, its use in infectious lesions, role in differentiating metastasis from gliomas, seizures and Alzheimer's disease. The most important use of MR Spectroscopy has been in differentiating recurrent gliomas from radiation necrosis.

Most studies on MR Spectroscopy have been concentrated on the use of MR Spectroscopy in predicting tumor presence and on Neurological disorders like Alzheimer's, Schizophrenia. Only few studies have been done in differentiating ring enhancing lesions on CT with MR Spectroscopy which poses a clinical as well as radiological dilemma for the Neurosurgeon regarding management. The most commonly encountered ring enhancing lesions of the brain are high grade gliomas, metastasis, brain abscess, inflammatory lesions like tuberculomas, demyelinating diseases, resolving hematomas and cysticercosis.

In our study, we have also used MR Spectroscopy to differentiate grades of tumor. It was postulated that elevated choline may reflect an increase in the concentration of the spectroscopically detectable metabolites that are precursors of membrane phospholipids needed to support the increased cell turnover in neoplastic tissue reflecting increased cellularity and proliferation, higher membrane turnover or prolongation of T2 relaxation times

of choline containing compounds. Decreased NAA levels are attributed to the low density of neuronal cells. A decreased NAA/creatine ratio is consistent with the replacement of healthy neurons by neoplastic cells. Lactate, an end-product of anaerobic glycolysis, is often elevated in rapidly growing tumors, in which hypoxic regions may exist and lipid in areas of necrosis. In this study, choline was elevated in all gliomas along with increase in choline/creatine ratio.

In high grade anaplastic astrocytomas, moderate elevation in lipid were seen in all cases. In contrast to high grade gliomas, no cases with low grade gliomas showed lipid peak in consistent with finding from various published papers. In cases with GBM, all of which showed prominent lipid peaks along with moderate elevation of myoinositol levels which is in accordance with some published papers reporting decreased levels of myoinositol in glioblastoma cases which were confirmed histopathologically.

Myoinositol (mI), a molecule that is located within astrocytes, is presumed to act as an osmolyte, and its concentration is altered in many brain disorders. MI is also involved in the activation of protein C kinase. Protein C kinase leads to production of proteolytic enzymes, which are found more often in malignant and aggressive primary cerebral tumors. Thus, the levels of mI, as seen by magnetic resonance spectroscopy, may be helpful for predicting the histological grade of brain tumors. Mauricio Castillo in his paper found that a trend towards lower mI/Cr in higher-grade astrocytomas (Anaplastic and GBM) and higher MI/Cr in low-grade astrocytomas compared with healthy control subjects.

Tedeschi et al used choline as an indicator of the progression of neoplasm and showed that over a 3-1/2–year period, all progressive tumors had an increase in the choline concentration of over 45%, whereas all stable tumors showed a 35% increase or less. These results support our findings that choline and lactate are accurate markers for differentiating

among tumor grades.

In our study we have 6 cases of metastatic brain disease, all of which had high choline levels, high choline/creatine ratio along with prominent lactate and lipid peaks in similarity to high grade gliomas. All cases presented with typical irregular ring on contrast enhanced CT brain for whom MRS was done. Opstad et al prospectively recruited 47 patients with pathologically proven glioblastomas or metastases; 7 patients were later excluded due to poor quality spectra. The authors focused on the lipid peak-area ratio derived from single-voxel 1H-MR spectroscopy. They defined this as the ratio of L1 (the combined alanine, lactate, 1.4 macromolecule, and 1.3 lipid peak) to L2 (the combined 0.9 lipid and 0.87 macromolecule peaks). Using this ratio, they reported sensitivity and specificity equal to 80% at a threshold value of 2.9. He speculated that the difference in lipid profiles may be related to differences of membrane structure of infiltrative versus migratory tumor cells or to lipid metabolism.

We have four cases of meningiomas, one in intraventricular location, one in cerebellopontine angle and the other two were convexity meningiomas. Diagnosis of meningiomas on MRI is usually straight forward unless it is in intraventricular location where differential diagnosis of ependymoma, low grade gliomas must be considered. All cases showed alanine peak at 1.47ppm which invert on long TE sequences.

Alanine peak for meningiomas are considered as signature of meningiomas on MR Spectroscopy. The presence of alanine may indicate that the metabolism of meningiomas involves partial oxidation of glutamine rather than glycolysis. All cases had high choline peak with low NAA levels representing extramedullary origin of meningiomas. NAA is considered a neuronal marker found only in brain. NAA is absent in tumors originating outside the brain parenchyma and will only be detected if there is some tissue contamination from the adjacent

brain in the MRS voxel. Significantly, an unusually high ratio of Ala to Cr has been found in meningiomas because of the high Ala and low Cr content, and this is a relatively specific finding for meningiomas.

Abscess which typically produce ring enhancement on CT brain were evaluated with MR Spectroscopy as a part of research protocol. The diagnosis of pyogenic abscess was confirmed by aspiration of the pus. The pus was sent for culture and the AFB staining for acid fast bacilli. All the three cases of brain abscess we encountered were of pyogenic in nature. In our series we did not have tubercular abscess. The appearance of brain abscesses on MR imaging is nonspecific and does not suggest the specific etiologic agent responsible.[4,19,22] In all cases we had increased amino acid levels with lipid and lactate peaks in two of three cases.

Pyogenic brain abscesses in MR spectroscopy usually show the presence of amino acids at 0.9 ppm and lipid and lactate at 1.3 ppm, with or without the presence of acetate at 1.92 ppm and succinate at 2.4 ppm. The amino acids are always observed in pyogenic brain abscesses, even when the patient is being treated with antibiotics and repeated aspiration.

Pathologically, the pyogenic brain abscesses contain large amounts of neutrophils and proteins, which are released in the necrotic cavity. The breakdown of the neutrophils results in the release of large amount of proteolytic enzymes that hydrolyze the proteins into amino acids. This is the reason for detecting the amino acids (leucine, isoleucine, and valine) at 0.9 ppm in MR spectroscopy in pyogenic brain abscesses. On the other hand, tubercular abscesses teem with mycobacteria along with lymphocytes and a small number of neutrophils in the pus and necrotic brain tissue.

The mycobacteria are predominantly composed of lipids. There is a relative lack of proteolytic enzymes in the tuberculous inflammatory exudates compared with pyogenic

inflammation. Differentiation of tuberculous brain abscess from pyogenic abscess is important for management. Combined medical and surgical treatment (repeated aspirations) is recommended for the care of patients with pyogenic brain abscess, whereas surgical excision and antituberculous treatment are the norms for managing tuberculous brain abscess.

We have three cases of tuberculomas in our series, which were showing ring enhancement on CT contrast study and MRS showed prominent lipid peaks in all of them with corresponding T2 hypo intensity on MR imaging[16,17,22]. All cases were treated with anti-tuberculous therapy and showed resolution of the edema, contrast enhancement and mass lesion after 4 month period on CT contrast study. Intracranial tuberculomas show prominent lipid peaks[16,17] due to high lipid content in caseous material. Presence of serine is accepted as a distinct feature of tuberculomas. T2 shortening along with MRS features differentiates tuberculomas from other granulomatous processes (fungal and sarcoidosis) and metastatic neoplasms.

Our series includes one case of tumefactive multiple sclerosis which presented with irregular margins with ring like contrast enhancement on CT Brain. MRS done for the lesion showed increased choline, choline/creatine ratio, myoinositol and lactate-lipid peak. NAA was reduced. Choline is raised in acute plaques. The patient expired within days of treatment.

Multiple sclerosis is a chronic inflammatory disease of the CNS characterized by focal areas of demyelination. The mechanisms behind the destruction of myelin are still poorly understood. Reduced NAA is a putative indicator of persistent axonal damage, namely in chronic MS lesions. Moreover, choline containing compounds and myo-inositol were both found to be elevated within MS plaques, suggesting enhanced membrane turnover.[2,7,8,41] The rise of lactate within some lesions may correspond to the degree of inflammation, i.e., the

infiltration of macrophages in the acute episodes as seen also in other cerebral diseases.

Consistent with other studies of increased myoinositol levels in demyelinating and hypo myelinating diseases, the present findings of elevated myoinositol most likely represent both the accumulation of myelin breakdown products during acute phases and astrocytosis in demyelinated and remyelinated lesions.

In our series, we had one patient who presented with focal seizures, memory disturbance and headache with frontal release signs on examination. CT scan contrast study revealed a ring enhancing lesion in the dominant frontal region. MRS showed reduction of all metabolites. Reduction of all metabolites will be seen in hematomas and can be used to distinguish it from neoplastic lesions. Follow up CT brain after 2 months showed resolution of the hematoma.

We also had two cases of lymphoma which showed increased choline and prominent lipid lactate peaks. The spectroscopic appearance of lymphoma is similar to that of primary high-grade astrocytoma and metastases.[5] MR spectroscopy shows a marked elevation of choline and lipids and a significant reduction in creatine and NAA. MR spectroscopy is helpful in assessing the response of lymphoma to treatment; successfully treated lymphoma shows progressive decrease in choline and lipids.

CONCLUSION

Proton MR spectroscopy (^{1}H MRS) has been recognized as a safe diagnostic technique that can improve the noninvasive categorization of brain disorders and help in differentiating ring enhancing lesions seen on CT brain contrast study.

We have shown that specific metabolites are of diagnostic value in the division of tumors into three categories. Specifically, the lactate can be used to differentiate GBMs and anaplastic astrocytomas from low grade tumors. GBM can be identified in this group by high values of Lip 0.9 and Lip 1.3. These two broad resonances have been ascribed to necrotic regions in spectra and indicate a high grade of malignancy. The levels of choline, choline/creatine, NAA/creatine can be used to distinguish high-grade from low grade tumors. We found lower myoinositol in higher-grade tumors [GBM.].

Increase in alanine, defined as an inverted doublet centered at 1.47 ppm, has been found to be a consistent and relatively specific finding for meningiomas.

Metastases are high-grade brain lesions in which presence of necrosis, represented by broad resonances centered at 0.90 and 1.30 ppm were noted. Our study confirms a significant increase of these lipid resonances in metastasis, in contrast with lower-grade tumors. We did

not find any statistically significant difference between GBM and metastasis in the resonances defined in our study; accordingly, we considered them as a single group for classification purposes.

The conglomerate ring enhancement suggesting inflammatory rather than neoplastic along with central hypo intensity on T2 with prominent lipid peak is characteristic for tuberculomas.

The appearance of brain abscesses on MR imaging was nonspecific and does not suggest the specific etiologic agent responsible. Pyogenic brain abscesses on MR spectroscopy showed the presence of amino acids lipids and lactate. The amino acids were always observed in pyogenic brain abscesses.

BIBLIOGRAPHY

1) Arnold DL, Matthews PM, Francis G, Antel J. Proton magnetic resonance spectroscopy of human brain in vivo in the evaluation of multiple sclerosis: assessment of the load of disease. Magn Reson Med 1990;14:154–159.
2) Arnold DL, Matthews PM, Francis GS, et al. Proton magnetic resonance spectroscopic imaging for metabolic characterization of demyelinating plaques. Ann Neurol 1992;31:435–41
3) Barkovich AJ. Brain tumors of childhood. In: Pediatric Neuroimaging. 2nd ed. New York: Raven; 1995:338–340
4) Bowen BC, Post MJD. Intracranial infection. In: Atlas SW,ed. Magnetic Resonance Imaging of the Brain and Spine. New York, NY: Raven Press; 1997: 501–538
5) Bruhn H, Frahm J, Gyngell ML, et al. Noninvasive differentiation of tumors with use of localized H-1 MR spectroscopy in vivo: initial experience in patients with cerebral tumors. Radiology. 1989;172:541
6) Castillo M, Kwock L, Scatliff JH, Gudeman S, Greenwood R. Proton MR spectroscopic characteristics of a presumed giant subcortical heterotopia. AJNR Am J Neuroradiol 1993;14:426–429
7) Chen CJ. Serial proton magnetic resonance spectroscopy in lesions of Balo concentric sclerosis. J Comput Assist Tomogr 2001;25:713–18
8) Davie CA, Hawkins CP, Barker GJ, et al. Serial proton magnetic resonance

spectroscopy in acute multiple sclerosis lesions. Brain 1994;117:49–58

9) Demaerel P, Johannik K, Van Hecke P, et al. Localized H-1 NMR spectroscopy in fifty cases of newly diagnosed intracranial tumors. J Comput Assist Tomogr 1991;15:67–76

10) Demaerel P. In vivo localized single-voxel proton magnetic resonance spectroscopy of intracranial tumors. Int J Neuroradiol 1997;3:94–110

11) Devos A, Lukas L, Suykens JA, et al. Classification of brain tumours using short echo time 1H MR spectra. J Magn Reson 2004;170:164–75

12) Fulham MJ, Bizzi A, Dietz MJ, et al. Mapping of brain tumor metabolites with proton MR spectroscopic imaging: clinical relevance. Radiology 1992;185:675–686

13) Gill SS, Thomas DG, Van Bruggen N, et al. Proton MR spectroscopy of intracranial tumors: in vivo and in vitro studies. J Comput Assist Tomogr 1990;14:497–504

14) Gober JR. Noninvasive tissue characterization of brain tumor and radiation therapy using magnetic resonance spectroscopy. Neuroimaging Clin North Am 1993;3:779–802

15) Go KG, Kamman RL, Mooyaart EL, et al. Localized proton spectroscopy and spectroscopic imaging in cerebral gliomas, with comparison to positron emission tomography. Neuroradiology 1995;37:198–206

16) Gupta RK, Roy R. MR imaging and spectroscopy of intracranial tuberculomas. Curr Sci 1999;76:783-788

17) Gupta RK, Roy R, Poptani H, et al. Finger printing of Mycobacterium tuberculosis in intracranial tuberculomas using in vivo, ex vivo and in vitro proton spectroscopy. Magn Reson Med 1996;36:829-833

18) Gupta R, Vastal D, Husain N, Chawla S, Prasad K, Roy R, Kumar R, Jha D, Husain M. Differentiation of tuberculous from pyogenic brain abscesses with in vivo proton MR spectroscopy and magnetization transfer MR imaging. A J N R 2001; 2 2:1503-1509

19) Haimes AB, Zimmerman RD, Morgello S, et al. MR imaging of brain abscess. AJNR Am J Neuroradiol 1989;10:279-291

20) Herminghaus S, Dierks T, Pilatus U, et al. Determination of histopathological tumor grade in neuroepithelial brain tumors by using spectral pattern analysis of in vivo spectroscopic data. J Neurosurg 2003;98:74–81

21) Houkin K, Kamada K, Sawamura Y, et al. Proton magnetic resonance spectroscopy (1H-MRS for the evaluation of treatment of brain tumors. Neuroradiology 1995;37:99–103

22) Jinkins JR, Gupta R, Chang KH, Carbajal-Rodriguéz J. MR imaging of central nervous tuberculosis. Radiol Clin North Am 1995;33:771-786

23) Kreis R, Ernst T, Ross BD. Development of the human brain: in vivo quantification of metabolite and water content with proton magnetic resonance spectroscopy. Magn Reson Med 1993;30:424–437

24) Kugel H, Heindel W, Ernestus RI, Bunke J, du Mesnil R, Friedmann G.

Human brain tumors: spectral patterns detected with localized H-1 MR spectroscopy. Radiology 1992;183:701–709

25) Laws ER. Imaging brain tumors: beyond three dimensions. Nat Med 1996;2:271–272

26) Luyten PR, Marien AJH, Heindel W, et al. Metabolic imaging of patients with intracranial tumors: H-1 MR spectroscopic imaging and PET. Radiology 1990;176:791–799

27) Majos C, Alonso J, Aguilera C, et al. Proton magnetic resonance spectroscopy ((1)H MRS) of human brain tumours: assessment of differences between tumour types and its applicability in brain tumour categorization. Eur Radiol 2003;13:582–91

28) McKnight TR, Lamborn KR, Love TD ET AL.Correlation of magnetic resonance spectroscopic and growth characteristics within Grades II and III gliomas. J Neurosurg 2007 Apr;106(4):660-6

29) McKnight TR, von dem Bussche MH, Vigneron DB, et al. Histopathological validation of a three-dimensional magnetic resonance spectroscopy index as a predictor of tumor presence. J Neurosurg 2002;97:794–802

30) Michealis T, Merboldt KD, Bruhn H, Dipl Math WH, Frahm J. Absolute concentrations of metabolites in the adult human brain in vivo: quantification of localized proton MR spectra. Radiology 1993;187:219–227

31) Miller BL. A review of chemical issues in 1H NMR spectroscopy: N-acetyl-L-aspartate, creatine, and choline. NMR Biomed 1991;4:47–52

32) Mishra AM, Gupta RK, Jaggi RS, et al. Role of diffusion-weighted imaging and in vivo proton magnetic resonance spectroscopy in the differential diagnosis of ring-enhancing intracranial cystic mass lesions. J Comput Assist Tomogr 2004;28:540–47

33) Moller-Hartmann W, Herminghaus S, Krings T, et al. Clinical application of proton magnetic resonance spectroscopy in the diagnosis of intracranial mass lesions. Neuroradiology 2002;44:371–81

34) Opstad KS, Murphy MM, Wilkins PR, et al. Differentiation of metastases from high-grade gliomas using short echo time 1H spectroscopy. J Magn Reson Imaging 2004;20:187–92

35) Ott D, Hennig J, Ernst T. Human brain tumors: assessment with in vivo proton MR spectroscopy. Radiology 1993;186:745–752

36) Poptani H, Gupta RK, Roy R, Pandey R, Jain VK, Chhabra DK. Characterization of intracranial mass lesions with in vivo protonMR spectroscopy. AJNR Am J Neuroradiol 1995;16:1593–1603

37) Preul MC, Caramanos Z, Collins DL, et al. Accurate, noninvasive diagnosis of human brain tumors by using proton magnetic resonance spectroscopy.Nat Med 1996;2:323–325

38) Rand SR, Prost R, Haughton V, et al. Accuracy of single-voxel proton MR spectroscopy in distinguishing neoplastic from non-neoplastic brain lesions.

AJNR Am J Neuroradiol 1997;18:1695–1704

39) Ricci PE, Pitt A, Keller PJ, Coons SW, Heiserman JE. Effect of voxel position on single voxel MR spectroscopy findings. A J N R 2000; 2 1: 367-374

40) Sanders JA. Magnetic resonance spectroscopy. In: Orrison WW, Lewine JD, Sanders JA, Harthshorne MF, eds. Functional Brain Imaging. St Louis: Mosby, 1995:419–467

41) Sijens PE, van Dijk P, Oudkerk M. Correlation between choline level and Gd-DTPA enhancement in patients with brain metastases of mammary carcinomas. Magn Reson Med 1994;32:549–555

42) Segebarth CM, Baleriaux DF, Luyten PR, den Hollander JA. Detection of metabolic heterogeneity of human intracranial tumors in vivo by H-1 NMR spectroscopic imaging. Magn Reson Med 1990;13:62–76

43) Soher BJ, Hurd RE, Sailasuta N, Barker PB. Quantitation of automated single-voxel proton MRS using cerebral water as an internal reference. Magn Reson Med 1996;36:335–339

44) Sutton LN, Wehrli SL, Gennarelli L, et al. High-resolution 1Hmagnetic resonance spectroscopy of pediatric posterior fossa tumors in vitro. J Neurosurg 1994;81:443–448

45) Tate AR, Majos C, Moreno A, et al. Automated classification of short echo time in vivo 1H brain tumor spectra: a multicenter study. Magn Reson Med 2003; 49:29–36

46) Traber F, Block W, Flacke S, et al. [1H-MR Spectroscopy of brain tumors in the course of radiation therapy: use of fast spectroscopic imaging and singlevoxel spectroscopy for diagnosing recurrence]. Rofo 2002;174:33–42

47) Usenius J-PR, Kauppinen RA, Vainio PA. Quantitative metabolite patterns of human brain tumors: detection by 1H NMR spectroscopy in vivo and in vitro. J Comput Assist Tomogr 1994;18:705–713

48) Van der Knaap MS, Ross B, Valk J. Uses of MR in inborn errors of metabolism. In: Kucharczyk J, Mosely M, Barkovich AJ, eds. Magnetic Resonance Neuroimaging. Boca Raton: CRC Press, 1994:245–318

PROFORMA

PATIENT DETAILS

NAME :

AGE :

SEX :

NEURORADIOLOGICAL DIAGNOSIS :

MR SPECTROSCOPY FINDINGS

METABOLITE LEVELS

1. Choline
2. creatine
3. NAA

Ratio

1. Choline/creatine
2. NAA/creatine

Elevated levels of (mark tick at box)

1. Alanine
2. Aminoacids
3. Myoinositol
4. Lipid – Lactate

Histopathological Diagnosis :

Comment :